Peer Review
Experimental Toxicology Division
N H E E R L

CUMULATIVE RISK

Development of Experimental Data for Evaluation of the Human Cumulative Exposure, Dose and Health Risks for Pyrethroid Insecticides

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Introduction

Pyrethroids are a family of pesticides that are neurotoxicants. They are one of the most common pesticides used in indoor environments. Under the Food Quality Protection Act, EPA is required to consider cumulative risks from pesticides and other substances acting by a common mode of action. Cumulative risk assessments examine mixtures of chemicals and their exposure by multiple routes. Pyrethroids fall into this category because they induce toxicity through a common mode of action by interacting with sodium channels in the nervous system, they are commonly found as a mixture, and routes of exposure include (oral, diet, hand-to-mouth), dermal and inhalation.

Goals

Incorporate PBPK modeling into a cumulative risk model for pyrethroid pesticides. This will be done by 1) developing exposure-dose-response models for individual and mixtures of pyrethroids in rodents and human tissues; 2) scaling the models for human exposures; 3) apply the human models to estimate cumulative risk to pyrethroids.

Methods

A. Develop predictive pharmacokinetic methods and models: 1) examine the in vitro metabolism of pyrethroids pesticides in rodent and human tissues and subcellular fractions; 2) incorporate the in vitro metabolic parameters into a preliminary PBPK model; 3) test the PBPK model with limited in vivo studies (oral and dermal studies).

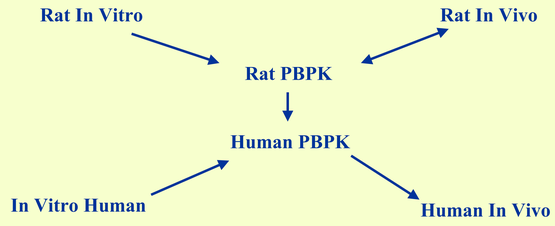
B. Develop Exposure-Dose-Response Models for individual pyrethroids: 1) determine in vivo target tissue concentrations of pyrethroids at time of effect measurement (neurotoxicity studies); 2) use PBPK and empirical modeling approaches to understand the relationship between tissue concentration and neurotoxic response (peak effect vs. AUC).

C. Combine individual PBPK models into a single model: 1) experimentally test the pharmacokinetic interactions and neurotoxic effects of mixtures of Type I and Type II pyrethroids; 2) test the PBPK model with the experimental data; 3) test for dose additivity.

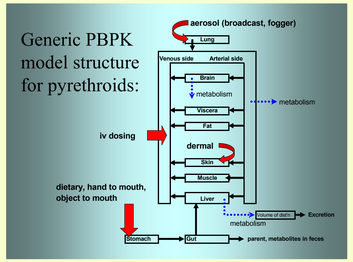
D. Scale the model for human exposure.

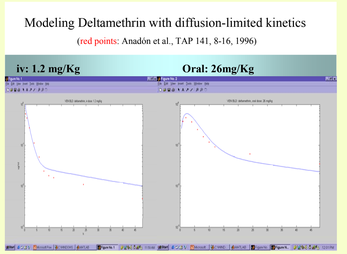
E. Apply the model to cumulative risk: 1) front the PBPK model with the Stochastic Human Exposure Dose Simulation (SHEDS) model developed by NERL and estimate human exposure and target tissue dose.

PBPK Model Development

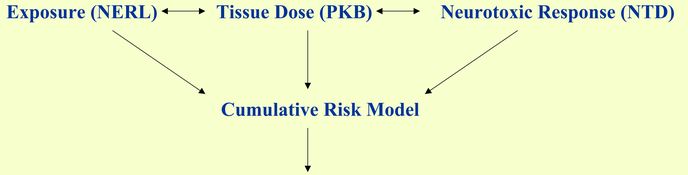


PBPK Model Structure for Pyrethroids





Flow of information and data between ORD Scientists



Impact

The data from this study will be the basis for the development of predictive pharmacokinetic models and will be an important component in the cumulative risk assessment for pyrethroid pesticides. Also, by using in vitro methodology combined with PBPK modeling, we will reduce the overall number of animals used in this study.

Future Directions

We plan to develop a biologically-based dose response model using the results from this study. Presently we will only be able to predict tissue concentrations using empirical methods. A greater understanding of the molecular metabolic and neurotoxic events of these pesticides will enable OPP to make more well-informed, scientific-based decisions on the risk for adverse effects from exposure to pyrethroid pesticides.

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